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Chlorhexidine Allergy: On the Rise and Often Overlooked

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Abstract

Purpose of Review In recent years, the risk of allergy to chlorhexidine is increasingly recognised. In this review, we discuss why the allergy is so easily overlooked and point out several preventative initiatives that can minimise the risk of both chlorhexidine sensitisation and allergy development and accidental re-exposure in patients with chlorhexidine allergy. Testing for chlorhexidine allergy is also discussed.

Recent Findings Numerous reports have been published from many different specialties. Symptoms range from mild skin symptoms to life-threatening anaphylaxis. Testing for chlorhexidine allergy is based on skin testing and in vitro testing. Recently, it was found that both skin prick testing and specific IgE have high sensitivities and specificities.

Summary This review gives an overview of chlorhexidine allergy with a special focus on preventative initiatives and testing.

Keywords Chlorhexidine · Chlorhexidine allergy · Skin testing · Specific IgE · Perioperative allergy · Allergy testing

Introduction

Chlorhexidine is an effective antiseptic used in the health care sector and in private homes all over the world (Fig. 1). In high doses, chlorhexidine can be toxic and cause damage for instance to the middle ear and cornea, but chlorhexidine generally has a good safety profile [2]. However, allergic reactions are reported with increasing frequency. The reactions range from mild skin symptoms, over life-threatening anaphylaxis [3•] to fatal reactions [4].

Considering the widespread use of chlorhexidine, allergic reactions are rare, but due to a lack of knowledge about the allergenic potential, chlorhexidine may be overlooked as a potential cause. The problem is further compounded by the fact that chlorhexidine is used in many different formulations, making exposure difficult to avoid even when an allergy has been confirmed [5••].

Chlorhexidine can cause both immediate type (type I) and delayed type (type IV) allergic reactions. In this review we seek to update the reader on immediate type allergy to chlorhexidine with a special focus on identifying chlorhexidine as an allergen and on preventative initiatives.

The Danish Anaesthesia Allergy Centre (DAAC) is the National reference centre for the investigation of perioperative allergic reactions in Denmark. Since 1999 all referred patients have been tested for chlorhexidine allergy as part of investigations in DAAC. This review is based on the published literature within the field of chlorhexidine allergy combined with relevant observations from DAAC.

Chlorhexidine—a Widely Used Antiseptic

Chlorhexidine was discovered in the 1950s by Imperial Chemical Industries whilst the company was searching for anti-malarial drugs [6]. It is a highly effective antiseptic and is effective against bacteria, fungi and viruses [2]. The effectiveness of chlorhexidine was shown in a recent meta-analysis including more than 5000 patients, where it was found that chlorhexidine reduced surgical-site infection significantly better than povidone-iodine, another commonly used antiseptic

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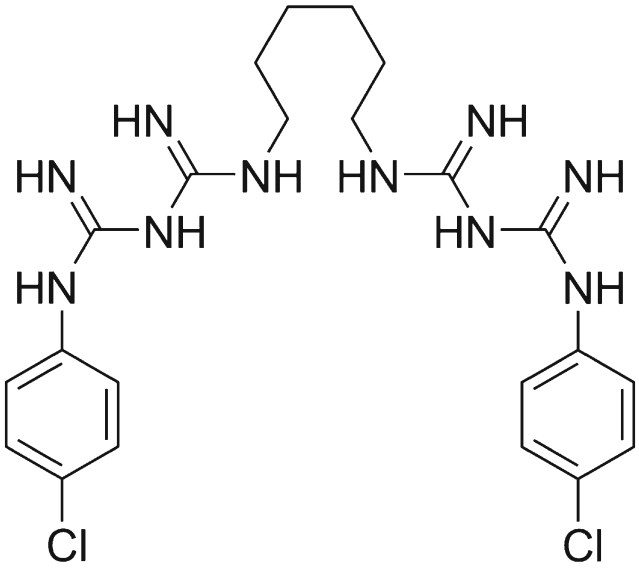

Fig. 1 The chemical structure of chlorhexidine ($C_{22}H_{30}Cl_2N_{10}$) (1)

(pooled odds ratio 0.68, 95% confidence interval 0.50–0.94) [7]. As a consequence of the superb antiseptic properties and a very favourable safety profile, chlorhexidine is increasingly used and can be found in many different products in the health care setting [8, 9]. According to the Australian Register of Therapeutic Goods, chlorhexidine can be found in 157 products in Australia [10•]. In the UK and USA reports have also revealed an extensive use of chlorhexidine in many different products [9, 11]. In 2015, we investigated the use of chlorhexidine in the hospitals in the Capital Region of Denmark and identified 42 chlorhexidine containing products distributed from the pharmacy. The products were marketed in different concentrations for several different sites of application: The oral cavity (in concentrations from 0.1–0.2% in mouth washes to 1–2% in dental gels), the urinary tract (in concentrations from 0.02% in bladder irrigation to 0.05% in generic urethral gels and commercially available products such as Instillagel® and Cathejell®), the vagina (in a concentration of 1% in a cream), the eyes (in a concentration of 0.02% in eye drops), and on the skin (in concentrations from 0.05 to 4% in skin disinfectants in preparations such as powder, scrubs, creams, and dressings) [8]. In addition, chlorhexidine is also found in non-drug formulations and medical devices such as central venous catheters and disinfectant skin swabs [8, 9]. In Denmark, the most commonly used products containing chlorhexidine are urethral gels, skin cleansing wipes and mouth washes.

Importantly, chlorhexidine is used not only in the health care setting but also as a preservative in some cosmetic products. In a recent market survey in Denmark, it was found that 3.6% of more than 2000 cosmetic products contained chlorhexidine [12]. To our knowledge, chlorhexidine in cosmetic products has never caused an allergic reaction, but it is unclear whether it can cause sensitisation.

Chlorhexidine Allergy on the Rise

Allergy to chlorhexidine was first described in 1984 in Japan in a 9-year-old boy who developed anaphylactic shock during surgery [13]. In subsequent years, several case reports from Japan were published emphasising the risk of allergic reactions (14–18). As a consequence, the Japanese Ministry of Welfare in 1984 recommended that the use of chlorhexidine on mucous membranes should be prohibited and that only a concentration of 0.05% should be used on wound surfaces [14]. These recommendations are clearly not followed today.

In recent years, the risk of chlorhexidine allergy has been increasingly recognised [19•, 20•, 21, 22], especially in the perioperative setting. Numerous reports of reactions have been published from all over the world from many different surgical specialties, e.g. urology [20•, 23, 24], orthopaedic surgery [25–28], thoracic surgery [11, 26], vascular surgery [10, 29], neurosurgery [30], gynaecology [31], gastrointestinal surgery [31, 32] and otorhinolaryngology [33] as well as in dentistry [4, 34, 35] and non-surgical specialties such as nephrology [36], paediatrics [37, 38] and neurology [39].

The majority of patients with chlorhexidine allergy are men, but the exact prevalence of chlorhexidine allergy is largely unknown, but it is thought to be low in the general population [22, 40••, 41••]. However, amongst patients who have experienced a suspected perioperative allergic reaction—a setting where exposure to chlorhexidine is almost unavoidable—the prevalence is much higher. In some countries, e.g. in UK, Denmark and Belgium, all patients with a suspected perioperative allergic reaction are tested for chlorhexidine allergy. In UK, the 6th National Audit Project (NAP6) included a total of 266 patients with suspected perioperative anaphylaxis from all NHS hospitals in 2016 and the results showed that chlorhexidine was the culprit drug in 9% of cases [42]. In Denmark, chlorhexidine was found to be the culprit drug in 22 out of 228 patients (10%) investigated for a suspected perioperative allergic reaction from 2004 to 2012 [40••] including both anaphylaxis and less severe allergic reactions. In Belgium, in a Flemish referral centre, chlorhexidine was the culprit drug in 22 out of 246 patients (9%) with a verified perioperative allergic reaction from 2001 to 2011 [43]. As a consequence, recent recommendations are that chlorhexidine should be tested in all patients with suspected perioperative allergic reactions [44, 45].

As a consequence of the increased awareness of chlorhexidine allergy, its rarity and the subsequent potential for an allergy to be overlooked, warnings have been issued from the authorities in several different countries in recent years. In 2012, the Therapeutic Goods Administration under the Department of Health in Australia issued a safety update highlighting the risk of anaphylaxis caused by chlorhexidine in central venous catheters [46]. In 2013, New Zealand Medicines and Medical Devices Safety Authority warned

against the risk of allergic reactions caused by chlorhexidine and encouraged health care professionals to report all anaphylactic reactions to products containing chlorhexidine to the Centre for Adverse Reactions Monitoring [47]. In 2014, The Medicines and Healthcare products Regulatory Agency in the United Kingdom issued an alert regarding the risk of anaphylactoid reactions caused by chlorhexidine in medical devices and medicinal products (48). In 2016, Health Canada evaluated the risk of chlorhexidine allergy and determined that topical chlorhexidine may cause anaphylactic reactions [49]. In 2017, The Food and Drug Administration in the USA issued a warning about rare but serious allergic reactions with the skin antiseptic chlorhexidine gluconate [50]. Altogether, these warnings emphasise that chlorhexidine allergy is increasingly recognised and there is a need for improving awareness of the use of and allergenic potential of chlorhexidine.

Many different substances have structures which resemble parts of the chlorhexidine molecule. Although cross-reactivity can be a theoretical possibility, there is currently no convincing evidence that this is a problem.

Are Health Care Workers at Risk of Developing Chlorhexidine Allergy?

Despite the widespread use of chlorhexidine in the health care setting, only few case reports have reported chlorhexidine allergy in health care workers [51–53, 54•, 55•]. To investigate the risk amongst health care workers, three small prospective studies have been conducted with ambiguous results. In 2009, Nagendran et al. distributed 86 questionnaires to health care workers from surgical wards, theatres, accident and emergency, maternity, dental and endoscopy units in UK. A total of 53 agreed to participate in the study and had allergy tests performed. Overall, four of the 53 were diagnosed with chlorhexidine allergy [55•]. In contrast to these findings are the results from two studies from Denmark. In 2016, Ibler et al. included a total of 120 health care workers with hand eczema and found one person with a positive skin prick test, but all specific IgE tests were negative [56]. In 2002, Garvey et al. investigated a total of 104 health care workers from a hospital in the Capital Region of Denmark with skin prick testing and intradermal testing—all tests were negative [57]. Differences in exposure patterns and the concentrations of chlorhexidine used may contribute to the variation in sensitised personnel. In UK, infection control guidelines recommend the use of 2% chlorhexidine in specific clinical settings, whereas a concentration of 0.5% is used in most products in Denmark [55•, 57]. Altogether, however, the exact risk of chlorhexidine allergy amongst health care workers remains unclear and larger studies are needed to elucidate this further. Interestingly, the overall number of reported cases is low. It could be speculated that in spite of the widespread use in the health care setting, health care workers have only limited direct exposure to chlorhexidine usually by hand disinfection of intact skin.

Exposure Routes for Chlorhexidine and Reasons Why Chlorhexidine Allergy Is Easily Overlooked

Chlorhexidine Allergy Is Easily Overlooked for Several Reasons

Firstly, milder symptoms attributed to chlorhexidine may be overlooked. At the time of diagnosis many chlorhexidine allergic patients report, retrospectively, that they have had previous mild allergic reactions which can be related to chlorhexidine exposure [3•, 58]. These reactions may include localised itching, redness and swelling after blood sampling or intravenous access, or a postoperative urticarial reaction (see Fig. 2) [23]. These symptoms are frequently either overlooked or dismissed as unimportant by health care workers and the patients themselves. However, a high index of suspicion of chlorhexidine allergy and referral for allergy investigation, even after relatively mild reactions, could save the patient from additional exposure and potentially more severe allergic reactions.

Secondly, and perhaps most importantly, exposure to chlorhexidine is often not recognised and chlorhexidine is not suspected when allergic symptoms appear, especially in the health care setting. During surgery and anaesthesia, most patients are exposed to chlorhexidine in many different products, and the majority of allergic reactions to chlorhexidine take place in this setting. Perioperative allergic reactions are rare but often present with sudden and unexpected onset of severe symptoms, requiring rapid recognition and treatment. Perioperative allergic reactions to chlorhexidine are often severe, may be life-threatening and usually present with multiorgan involvement and in rare cases even cardiac arrest [40••,

Fig. 2 Postoperative urticaria can be a sign of chlorhexidine allergy and should lead to allergy investigations. Reprinted with permission from journal [23]

59••]. In patients who are exposed to chlorhexidine intravenously, e.g. during insertion of a chlorhexidine-coated central venous catheter, symptoms usually occur few minutes after exposure [60]. However, chlorhexidine exposure is more often on the skin, prior to surgical incision, or on mucous membranes mostly in the urinary tract via urethral gels. These exposures lead to a delay in symptom onset ranging from 10 to 50 min after administration, and exposure to chlorhexidine may not be linked to the allergic reaction or may be missed altogether [61].

After a perioperative allergic reaction, it is tempting to guess the culprit drug based on the time of administration of each drug, but this is discouraged as the correct allergen is missed in a high number of patients [62, 63]. Reactions to chlorhexidine may present at the time when prophylactic antibiotics are administered and the reaction may erroneously be attributed to the antibiotic, leading to chlorhexidine being overlooked as the true allergen [23]. This may have very severe consequences for the patient during subsequent surgery due to a high risk of a potentially more severe reaction on re-exposure. Patients with perioperative allergic reactions should therefore always be referred for allergy investigation, preferably in a specialised centre with collaboration between allergists and anaesthesiologists, as identifying the culprit is difficult due to exposure to many different drug and substances [19]. As perioperative exposure to chlorhexidine is almost inevitable in many countries, all patients with perioperative allergic reactions should be tested with chlorhexidine [44, 45, 58]. Unfortunately, routine testing is still not performed in all centres due to lack of awareness of chlorhexidine as an allergen.

Notably, although all products containing chlorhexidine have the potential to cause allergic reactions, it appears that some products more frequently cause allergic reactions than others. Especially two products deserve special attention as the majority of reactions to chlorhexidine are attributed to either of these: the urethral gel and the chlorhexidine impregnated central venous catheter. In 2016, Sharp et al. reviewed the literature on chlorhexidine allergy in surgical patients and found that chlorhexidine in urethral gels attributed to 30 of 68 and chlorhexidine coated central venous catheters attributed to 26 of 68 published case reports, highlighting the allergenic potential in these gels and catheters [3•]. In 2016, we followed up 23 patients diagnosed with chlorhexidine allergy in the Danish Anaesthesia Allergy Centre during 1999–2015. Two accidental re-exposures to chlorhexidine in urethral gels were reported, highlighting how easy it is to miss that these gels contain chlorhexidine [5••]. Urethral gels serve as a lubricant and contain both local anaesthetics and chlorhexidine. This 'hidden' exposure to chlorhexidine is easily missed and poses a particular problem for patients with chlorhexidine allergy: unlike regular drug allergy, where the culprit drug is always prescribed by a medical doctor, chlorhexidine in urethral gels can be administered by other health care workers, e.g. nurses and health care assistants. Consequently, awareness of chlorhexidine allergy is not only relevant for medical doctors but for all health care workers who are in contact with the patient [64].

Regarding the central venous catheters, several reports have highlighted the risk caused by these catheters. In the 6th National Audit Project (NAP6) in UK, where data on all patients with perioperative anaphylaxis from all NHS hospitals in 2016 were collected, it was reported that in two patients subsequently diagnosed with chlorhexidine allergy, the chlorhexidine coated central venous catheter was not removed during the allergic reaction, highlighting how easy this exposure is overlooked. Consequently, the authors recommend that the central venous catheter should be removed when anaphylaxis occurs shortly after insertion [42, 44]. Moreover, chlorhexidine content can be difficult to identify on the package and this is described as a problem in several case reports [60, 65].

Interestingly, despite the widespread use of chlorhexidine as an oral antiseptic, only few reports have described patients who have reacted when exposed to chlorhexidine in the oral cavity [4]. The case reports primarily describe patients who have reacted after exposure to chlorhexidine on broken mucous membranes for instance after tooth extraction, as well as reactions to dental gels containing a relatively high concentration of chlorhexidine. Despite the low number of reactions caused by oral antiseptics, these products can cause very severe reactions and fatalities have been reported in this setting [4]. It remains unclear why there is this large discrepancy between the high number of reports on patients who have reacted when exposed in urethra compared with the low number of patients who have reacted when exposed in the oral cavity. The mucous membrane in the oral cavity is adapted to tolerate exposures to a multitude of substances and it may also be less permeable for chlorhexidine than the urethral mucous membrane. However, to our knowledge the absorption of chlorhexidine from different mucosal surfaces in man has never been investigated.

Thirdly, chlorhexidine is not recognised as a potential allergen by health care workers. Chlorhexidine is very well tolerated in most patients and chlorhexidine allergy is relatively rare; therefore, health care workers associate the use of chlorhexidine with the positive antimicrobial effects and do not suspect adverse effects, such as allergy. As a result there is generally little awareness of chlorhexidine content in medical products and devices. This means that there is limited experience with which products to avoid when treating chlorhexidine allergic patients. In fact, in a Danish follow-up study it was recently shown that approximately 1/3 of patients diagnosed with chlorhexidine allergy after a perioperative allergic reaction had been accidentally re-exposed to chlorhexidine on a later occasion, leading to an allergic reaction [5••].

Table 1 Preventative initiatives in chlorhexidine allergy

What can be done to minimise the risk of sensitisation to chlorhexidine?
Chlorhexidine should only be used in products when necessary and in the minimum effective concentration
Chlorhexidine should not be used routinely in urethral gels
Future research should focus on defining when chlorhexidine is needed for skin disinfection and for use on central venous catheters and on estimating the minimum effective concentration to balance the risk of infection with the risk of sensitisation
What can be done to minimise the risk of overlooking chlorhexidine allergy?
Health care professionals should be aware of the allergy and suspect chlorhexidine allergy in patients with allergic reactions in the health care setting
All patients with a perioperative or periprocedural allergic reaction should be tested for chlorhexidine allergy
All patients with a mild or unspecific reaction after exposure to chlorhexidine should be tested for chlorhexidine allergy. This includes patients with local redness or swelling after blood sampling, a postoperative urticarial reaction or swelling of genitalia after urethral catherisation
In the pre-anaesthetic assessment all patients should be directly questioned about previous symptoms on exposure to chlorhexidine for instance after using mouth washes, skin antiseptics and urethral gels or in the health care setting in general
What can be done to minimise the risk of accidental re-exposure in a chlorhexidine allergic patient?
Increased awareness about chlorhexidine allergy amongst health care workers
Patient vigilance and questioning of health care workers about potential exposures
All products containing chlorhexidine should be clearly labelled
A list of all products containing chlorhexidine should be available in health care facilities and optionally each facility could have boxes containing chlorhexidine-free products

Prevention

We believe that several initiatives can minimise the risk of developing chlorhexidine allergy, of overlooking chlorhexidine allergy and avoiding accidental re-exposure in patients diagnosed with chlorhexidine allergy (see Table 1).

What Can Be Done to Decrease the Risk of Sensitisation to Chlorhexidine?

The risk of sensitisation to chlorhexidine increases with repeated exposure, and probably, the risk is also increased with exposure to higher concentrations [36]. As a general rule therefore, disinfection with chlorhexidine should only be used when necessary, i.e. where a beneficial effect has been proven, and in the lowest effective concentration. Across countries, many different products contain chlorhexidine in various concentrations. In Denmark, skin disinfection, for all procedures, is performed with chlorhexidine in a concentration of 0.5%, whereas in UK, national guidelines recommend skin disinfection with 2% chlorhexidine before insertion of a central or peripheral vascular access device [8, 36, 66]. It is unclear why the concentration varies between countries and the reasoning for using a 2% concentration of chlorhexidine is unclear. In 2012, Nishihara investigated the reduction in microbial populations in the inguinal, abdominal and antecubital sites in 74 volunteers after skin cleansing with chlorhexidine in different concentrations, and the results showed no stronger reduction in microbial populations when using a 1% chlorhexidine solution compared with a 2% chlorhexidine solution, which questions the rationale for using a 2% chlorhexidine solution for skin disinfection. In addition, it can be discussed whether chlorhexidine should be included routinely for all skin disinfection. For instance, is chlorhexidine disinfection really necessary prior to routine blood sampling?

Also, it can be discussed whether chlorhexidine is needed in urethral gels. In 2015, Stewart et al. reported that the European Association of Urology recommended against the use of topical antiseptic or antimicrobials to the catheter, urethra or meatus, and in the updated guideline from 2018, this is still recommended [10•, 67, 68]. Consequently, in Australia and in UK, a urethral gel without chlorhexidine has been introduced [10•, 69]. However, in many countries including Denmark, chlorhexidine is still used routinely in urethral gels [8].

In some countries central venous catheters are coated with chlorhexidine and severe allergic reactions to chlorhexidine, on insertion, have been reported in the literature [18, 32, 60, 65, 70, 71]. Infections originating from these catheters—especially blood stream infections—are an important clinical problem leading to significant morbidity and mortality. However, it can be questioned whether chlorhexidine coating is the right answer to this problem as benefit should always outweigh risk in this type of decision. Indeed, a Cochrane review from 2017 found that central venous catheters coated with minocycline-rifampicin reduced the risk of blood stream infection significantly better than chlorhexidine (relative risk 0.38 (95% confidence interval 0.21–0.71)) (72), so it could be speculated that other alternatives are better than chlorhexidine. In UK, antimicrobial-impregnated central venous catheters are recommended in patients whose CVC is expected to remain in place for more than 5 days, whereas in the USA, the Center for Disease Control and Prevention recommend CVCs coated with either chlorhexidine or minocycline-rifampicin in these

patients [66, 73]. However, as there may be problems with potential allergy and antimicrobial resistance to the antibiotics further research should be carried out to investigate the best possible coating of central venous catheters [66]. In addition, research is needed to further explore the need for chlorhexidine disinfection and the minimum effective concentration in different clinical settings.

What Can Be Done to Minimise the Risk of Overlooking Chlorhexidine Allergy?

Increasing awareness of chlorhexidine allergy in health care workers is an important step. In addition, referral of patients with mild allergic symptoms or unspecific reactions after chlorhexidine exposure and patients with suspected perioperative or periprocedural allergic reactions for investigation for chlorhexidine allergy will increase the chances of making the diagnosis. Direct questioning of the patient about localised allergic symptoms such as itching and swelling on contact with disinfectants on the skin, e.g. during venepuncture or intravenous access or unexplained/uninvestigated urticaria after surgery or invasive procedures such as coronary arteriographies and dental procedures or even swelling of genitalia after a urethral catheter, will increase chances of identifying chlorhexidine allergic patients before re-exposure and potentially more severe reactions.

What Can Be Done to Minimise the Risk of Accidental Re-Exposure in Chlorhexidine Allergic Patients?

Minimising the risk of accidental re-exposure is paramount, and it is important that all health care workers are aware of possible sources of chlorhexidine when in contact with a chlorhexidine allergic patient. The Australian and New Zealand Anaesthetic Allergy Group (ANZAAG) recommends that health care facilities have a current register of products that contain chlorhexidine [74].

At the time of diagnosis of chlorhexidine allergy patients should be informed thoroughly about which products contain chlorhexidine both in the home and in the health system. Interestingly, none of the patients followed up after their diagnosis with chlorhexidine allergy in the Danish Anaesthesia Allergy Centre accidentally re-exposed themselves to chlorhexidine, but 1/3 were accidentally re-exposed on contact with the health system. This emphasises the need for the patient to notify health care workers about their chlorhexidine allergy, but also to be extremely vigilant and ask health care workers to double-check for content of chlorhexidine before exposing the patient to any product or procedure. All products containing chlorhexidine should be clearly labelled and this is far from the case at the present time. On some products, chlorhexidine is labelled with tiny letters and in some cases abbreviations such as CHX or CHG (chlorhexidine digluconate) are used. There are many similarities with latex allergy but latex is clearly labelled on all medical devices with its own packaging symbol. A similar approach could be considered for chlorhexidine. It has been suggested to have chlorhexidine-free boxes with chlorhexidine-free products placed in hospitals like is the case for latex. Indeed, chlorhexidine-free alternatives such as chlorhexidine-free central venous catheters, single-use isopropyl alcohol 70% wipes, alcoholic povidone-iodine solution for surgical skin preparation and sterile water-based lubricant for urethral catherisation have been included in the 'anaphylaxis management box' in a hospital in UK [75]. Ideally, a list of all products containing chlorhexidine and of chlorhexidine-free alternatives should be available in health care facilities. Such a list has to be based on local product availability and should be updated regularly as availability varies across countries and health care facilities, and changes over time.

Testing for Chlorhexidine Allergy

All patients with suspected chlorhexidine allergy, i.e. allergic symptoms either localised or systemic in connection with certain or suspected chlorhexidine exposure, in the home or health care setting should be investigated by specialists with expertise in this allergy. It is also recommended that all patients with a suspected perioperative or periprocedural allergic reaction are tested for chlorhexidine allergy.

Although an oral provocation model has recently been proposed in a chlorhexidine allergic patient who reacted during a dental procedure [35], the oral mucosa may not be the best model for provocation as mentioned earlier. Currently, a validated challenge model is not available for both technical and ethical reasons. Most chlorhexidine allergic patients experience perioperative allergic reactions, potentially with multiple simultaneous exposures (e.g. urethra, venepuncture, skin incision) in differing concentrations which is impossible to mimic. Most reactions are reported after urethral exposure or via direct entry in the bloodstream (via central venous catheters) and re-exposure using these routes is likely to be unacceptable to the patient. In addition, there is no knowledge of amount or concentration to use for either route and there would be a significant risk of inducing anaphylaxis during provocation. Chlorhexidine allergic patients have often experienced severe reactions leading to anxiety in the patient and a reluctance to be re-exposed, regardless of the route. As a consequence, the diagnosis is currently based on results from skin testing and in vitro testing. For these tests, and especially for combinations of tests, high sensitivities and specificities have been demonstrated, making them very useful when testing for chlorhexidine allergy [40••].

The following tests can be performed: in vivo testing including skin testing (skin prick testing and intradermal testing) which should always be performed in the light of a negative control with saline and a positive control with histamine [41••]

and in vitro testing including specific IgE and histamine release testing/basophil activation testing.

Skin Prick Testing

For skin prick testing, in DAAC a concentration of 5 mg/ml has been used since 1999, and in 2013, this concentration was endorsed by the European Network for Drug Allergy [59••, 76]. The skin prick test is considered positive if the diameter of the wheal is a minimum of 3 mm [77]. In DAAC it was observed early on that the skin prick test may have a delayed positive response of up to 30 min. This has been observed since and it is recommended that the skin prick test is read at minimum 20 min [31, 58]. A study from DAAC of 22 patients with chlorhexidine allergy out of 228 patients with suspected perioperative allergy found a very high sensitivity of 95% and specificity of 97% for skin prick testing alone [40••].

Intradermal Testing

For intradermal testing, a maximum non-irritative concentration of chlorhexidine digluconate of 0.002 mg/ml has been recommended from DAAC, and this has also been endorsed by the European Network for Drug Allergy [59••, 76]. To standardise the procedure, we recommend intradermal testing with a fixed volume of 0.02 ml injected into dermis with a 0.5-ml syringe creating a bleb of 3–5 mm. The test is read at 20 min where the diameter of the wheal that has arisen from the bleb is measured. Several positivity criteria exist in different guidelines [77–79], but the criterion with the highest combined sensitivity and specificity is the development of a wheal with a diameter which is ≥ 3 mm greater than the negative control/diameter of the induced bleb.

Specific IgE Testing

Specific IgE can be measured using a commercially available assay (ImmunoCap®, Thermo Fisher Scientific) and the cut-off for a positive test, recommended by the manufacturer, is 0.35 kUA/l. In a study from DAAC, we have estimated the sensitivity and specificity to 100% and 97%, respectively using this cut-off [40••]. In Australia, Anderson et al. recently estimated the sensitivity and specificity to 84.2% and 93.7%, respectively [80•]. The latter study also found that an alternative cut-off of 0.20 kUA/l increased the sensitivity to 94.7% but slightly decreased the specificity to 90.1%.

It was recently shown that levels of specific IgE vary greatly over time and between patients [5••]. Although, in most patients, specific IgE is above the cut-off of 0.35 kUA/l at the time of the allergic reaction, the levels increase in the first few weeks to months after the reaction. Consequently, the optimal sampling time seems to be > 1 month and < 4 months after the reaction. After the initial increase, levels of specific IgE gradually decline—with very variable rates between patients—to below the cut-off of 0.35 kUA/l on lack of exposure, but this does not indicate loss of clinical reactivity. Indeed, it has been shown that accidental re-exposure in these patients can cause symptoms and renewed increase in specific IgE [5••]. Altogether, it is important to take time elapsed from the allergic reaction into consideration when interpreting specific IgE results.

Histamine Release Testing/Basophil Activation Testing

Histamine release testing has been investigated in one study on chlorhexidine allergic patients, and the sensitivity and specificity were estimated to be 55% and 99%, respectively. The basophil activation test (BAT) with chlorhexidine has only been investigated in one study, where the sensitivity was estimated to be 50% [41••]. Whilst specificity is high with these tests sensitivity is low and they are reliant on analysis within few hours of blood sampling for optimal results. This means that use of these tests is limited to specialised centres and use in situations where other test results do not lead to a firm conclusion.

How Is Chlorhexidine Allergy Diagnosed?

In DAAC, chlorhexidine allergy is diagnosed based on a relevant clinical reaction in the context of exposure to chlorhexidine in combination with a minimum of two positive diagnostic tests [40••]. This definition has previously been applied for Rocuronium, another drug for which a provocation model is not available [81]. If testing is negative in patients with a high suspicion of chlorhexidine allergy, we recommend that testing is repeated a few months later. We encourage future research to focus on evaluating this diagnostic approach in chlorhexidine allergy and the potential application for other drugs.

Conclusions

Chlorhexidine is an effective antiseptic and increasingly used in many different products in the health care setting. Probably as a consequence of increased use, chlorhexidine allergy is on the rise, but possibly still underestimated as the allergy is easily overlooked due to lack of awareness of the allergy and 'hidden' exposure in several products. During surgery and most invasive procedures outside the operating room, patients are exposed to chlorhexidine and all patients with suspected perioperative and periprocedural allergic reactions should therefore be tested for chlorhexidine allergy. Unfortunately, some chlorhexidine allergic patients are accidentally re-exposed after having been diagnosed with the allergy, resulting in additional severe allergic reactions. This

emphasises the need for increasing awareness amongst health care workers of chlorhexidine-containing products and ensuring that patients are vigilant when in contact with the health care system.

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Compliance with Ethical Standards

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References

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

1. The chemical structure of chlorhexidine. https://da.wikipedia.org/wiki/Fil:Chlorhexidine.png. Accessed 24 Feb 2019.
2. Lim KS, Kam PC. Chlorhexidine—pharmacology and clinical applications. Anaesth Intensive Care. 2008;36:502–12.
3.• Sharp G, Green S, Rose M. Chlorhexidine-induced anaphylaxis in surgical patients: a review of the literature. ANZ J Surg. 2016;86:237–43 **A systematic review on chlorhexidine allergy.**
4. Pemberton MN, Gibson J. Chlorhexidine and hypersensitivity reactions in dentistry. Br Dent J. 2012;213:547–50.
5.•• Opstrup MS, Poulsen LK, Malling HJ, Jensen BM, Garvey LH. Dynamics of plasma levels of specific IgE in chlorhexidine allergic patients with and without accidental re-exposure. Clin Exp Allergy. 2016;46:1090–8 **Study showing the dynamics of plasma levels in chlorhexidine allergy.**
6. Davies GE, Francis J, Martin AR, Rose FL, Swain G. 1:6-Di-4′-chlorophenyldiguanidohexane (hibitane); laboratory investigation of a new antibacterial agent of high potency. Br J Pharmacol Chemother. 1954;9:192–6.
7. Noorani A, Rabey N, Walsh SR, Davies RJ. Systematic review and meta-analysis of preoperative antisepsis with chlorhexidine versus povidone-iodine in clean-contaminated surgery. Br J Surg. 2010;97:1614–20.
8. Opstrup MS, Johansen JD, Garvey LH. Chlorhexidine allergy: sources of exposure in the health-care setting. Br J Anaesth. 2015;114:704–5.
9. Silvestri DL, McEnery-Stonelake M. Chlorhexidine: uses and adverse reactions. Dermatitis. 2013;24:112–8.
10.• Stewart M, Lenaghan D. The danger of chlorhexidine in lignocaine gel: a case report of anaphylaxis during urinary catheterisation. Australas Med J. 2015;8:304–6 **Case report discussing whether chlorhexidine is needed in urethral gels.**
11. Odedra KM, Farooque S. Chlorhexidine : an unrecognised cause of anaphylaxis. Postgrad Med J. 2014;90:709–14.
12. Opstrup MS, Johansen JD, Bossi R, Lundov MD, Garvey LH. Chlorhexidine in cosmetic products—a market survey. Contact Dermatitis. 2015;72:55–8.
13. Nishioka K, Doi T, Katayama I. Histamine release in contact urticaria. Contact Dermatitis. 1984;11:191.
14. Okano M, Nomura M, Hata S, Okada N, Sato K, Kitano Y, et al. Anaphylactic symptoms due to chlorhexidine gluconate. Arch Dermatol. 1989;125:50–2.
15. Ohtoshi T, Yamauchi N, Tadokoro K, Miyachi S, Suzuki S, Miyamoto T, et al. IgE antibody-mediated shock reaction caused by topical application of chlorhexidine. Clin Allergy. 1986;16:155–61.
16. Fujita S, Sumita S, Kawana S, Iwasaki H, Namiki A. Two cases of anaphylactic shock induced by chlorhexidine. Masui. 1997;46:1118–21.
17. Okuda T, Funasaka M, Arimitsu M, Umeda T, Wakita K, Koga Y. Anaphylactic shock by ophthalmic wash solution containing chlorhexidine. Masui. 1994;43:1352–5.
18. Oda T, Hamasaki J, Kanda N, Mikami K. Anaphylactic shock induced by an antiseptic-coated central venous [correction of nervous] catheter. Anaesthesiology. 1997;87:1242–4.
19. Garvey L. Old, new and hidden causes of perioperative hypersensitivity. Curr Pharm Des. 2016;22:6814–24.
20.• Rutkowski K, Wagner A. Chlorhexidine: a new latex? Eur Urol. 2015;68:345–7 **Review discussing the similarities between chlorhexidine and latex.**
21. Garvey LH, Hunter JM. Changing culprits in perioperative anaphylaxis. Br J Anaesth. 2018;121:114–7.
22. Nakonechna A, Dore P, Dixon T, Khan S, Deacock S, Holding S, et al. Immediate hypersensitivity to chlorhexidine is increasingly recognised in the United Kingdom. Allergol Immunopathol. 2014;42:44–9.
23. Opstrup MS, Garvey LH (2019) Chlorhexidine allergy: mild allergic reactions can precede anaphylaxis in the healthcare setting—a case report. Turk J Anaesthesiol Reanim; Accepted.
24. Koch A, Wollina U. Chlorhexidine allergy. Allergo J Int. 2014;23:84–6.
25. Dick AG, Dhinsa B, Walker RP, Singh S. Delayed allergic reaction to ChloraPrepTM in foot and ankle surgery. J Foot Ankle Surg. 2018;58:2018–20.
26. Postolova A, Bradley JT, Parris D, Sherr J, McGhee SA, Hernandez JD. Anaphylaxis to invasive chlorhexidine administration despite tolerance of topical chlorhexidine use. J Allergy Clin Immunol Pract. 2018;6:1067–1069.e1.
27. Kow RY, Low CL, Ruben JK, Zaharul-Azri MZ, Ng MS. Life-threatening chlorhexidine anaphylaxis: a case report. Malaysian Orthop J. 2017;11:72–4.
28. Hong CC, Wang SM, Nather A, Tan JH, Tay SH, Poon KH. Chlorhexidine anaphylaxis masquerading as septic shock. Int Arch Allergy Immunol. 2015;167:16–20.
29. Totty J, Forsyth J, Mekako A, Chetter I. Life-threatening intraoperative anaphylaxis as a result of chlorhexidine present in Instillagel. BMJ Case Rep. 2017. https://doi.org/10.1136/bcr-2017-221443.
30. Wang ML, Chang CT, Huang HH, Yeh YC, Lee TS, Hung KY. Chlorhexidine-related refractory anaphylactic shock: a case successfully resuscitated with extracorporeal membrane oxygenation. J Clin Anesth. 2016;34:654–7.
31. Spoerl D, Jandus P, Harr T. Pitfalls and peculiarities in chlorhexidine allergy. J Allergy Clin Immunol Pract. 2016;4:991–2.

32. Weng M, Zhu M, Chen W, Miao C. Case report life-threatening anaphylactic shock due to chlorhexidine on the central venous catheter : a case series. Int J Clin Exp Med. 2014;7:5930–6.
33. Teixeira de Abreu AP, Ribeiro de Oliveira LR, Teixeira de Abreu AF, Ribeiro de Oliveira E, Santos de Melo Ireno M, Aarestrup FM, et al. Perioperative anaphylaxis to chlorhexidine during surgery and septoplasty. Case Rep Otolaryngol. 2017. https://doi.org/10.1155/2017/9605804.
34. Kofod C, Eriksen S, Garvey LH. Anafylaktisk shock udløst af klorhexidinskylning hos tandlæge. Tandlægebladet. 2017;121:336–9.
35. Gu JQ, Liu S, Zhi YX. Provocation test—confirmed chlorhexidine—induced anaphylaxis in dental procedure. Chin Med J. 2018;131:2893–4.
36. Bahal S, Sharma S, Garvey LH, Nagendran V. Anaphylaxis after disinfection with 2% chlorhexidine wand applicator. BMJ Case Rep. 2017. https://doi.org/10.1136/bcr-2017-219794.
37. Cogné Y, Mouton-Faivre C, Cavasino T, Teychene AM, de Pontual L, Dewachter P. Chlorhexidine-induced IgE-mediated allergy in a 6-year-old child. J Allergy Clin Immunol Pract. 2017;5:837–8.
38. Lasa EM, González C, García-Lirio E, Martínez S, Arroabarren E, Gamboa PM. Anaphylaxis caused by immediate hypersensitivity to topical chlorhexidine in children. Ann Allergy Asthma Immunol. 2017;118:118–9.
39. Mushtaq U, Tan A, Tan JA, Smith WB. Acute allergic reaction after intravenous saline injection: an unusual presentation of chlorhexidine allergy. Med J Aust. 2014;200:599–600.
40.•• Opstrup MS, Malling H-J, Krøigaard M, Mosbech H, Skov PS, Poulsen LK, et al. Standardized testing with chlorhexidine in perioperative allergy—a large single-centre evaluation. Allergy. 2014;69:1390–6 **A study investigating the value of the diagnostic tests in chlorhexidine allergy.**
41.•• Egner W, Helbert M, Sargur R, Swallow K, Harper N, Garcez T, et al. Chlorhexidine allergy in four specialist allergy centres in the United Kingdom, 2009–13: clinical features and diagnostic tests. Clin Exp Immunol. 2017;188:380–6 **A study characterizing patients with chlorhexidine allergy and evaluating the diagnostic tests in the United Kingdom.**
42. Harper NJN, Cook TM, Garcez T, Farmer L, Floss K, Marinho S, et al. Anaesthesia, surgery, and life-threatening allergic reactions: epidemiology and clinical features of perioperative anaphylaxis in the 6th National Audit Project (NAP6). Br J Anaesth. 2018;121:159–71.
43. Leysen J, De Witte L, Bridts CH, Ebo DG. Anaphylaxis during general anaesthesia : a 10-year survey 1 at the University Hospital of Antwerp. P Belg Roy Acad Med. 2013;2:88–100.
44. Harper NJN, Cook TM, Garcez T, Lucas DN, Thomas M, Kemp H, et al. Anaesthesia, surgery, and life-threatening allergic reactions: management and outcomes in the 6th National Audit Project (NAP6). Br J Anaesth. 2018;121:172–88.
45. Scolaro RJ, Crilly HM, Maycock EJ, McAleer PT, Nicholls KA, Rose MA, et al. Australian and New Zealand Anaesthetic Allergy Group perioperative anaphylaxis investigation guidelines. Anaesth Intensive Care. 2017;45:543–55.
46. The Therapeutic Goods Administration safety update on the risk of anaphylaxis caused by chlorhexidine in central venous catheters. https://www.tga.gov.au/publication-issue/medicines-safety-update-volume-3-number-3-june-2012. Accessed 24 Feb 2019.
47. Warning from New Zealand. https://medsafe.govt.nz/profs/PUArticles/June2013Chlorhexidine.htm. Accessed 24 Feb 2019.
48. The Medicines and Healthcare products Regulatory Agency alert regarding the risk of anaphylactoid reactions caused by chlorhexidine in medical devices and medicinal products. https://www.gov.uk/drug-device-alerts/medical-device-alert-all-medical-devices-and-medicinal-products-containing-chlorhexidine-risk-of-anaphylactic-reaction-due-to-chlorhexidine-allergy. Accessed 24 Feb 2019.
49. The risk of chlorhexidine allergy evaluated by Health Canada. https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/safety-reviews/summary-safety-review-topical-antiseptic-non-prescription-chlorhexidine-products-potential-risk.html. Accessed 24 Feb 2019.
50. FDA warning of serious allergic reactions caused by chlorhexidine. https://www.fda.gov/drugs/drugsafety/ucm530975.htm. Accessed 24 Feb 2019.
51. Toletone A, Dini G, Massa E, Bragazzi NL, Pignatti P, Voltolini S, et al. Chlorhexidine-induced anaphylaxis occurring in the workplace in a health-care worker: case report and review of the literature. Med Lav. 2018;109:68–76.
52. Vu M, Rajgopal Bala H, Cahill J, Toholka R, Nixon R. Immediate hypersensitivity to chlorhexidine. Aus J Dermatol. 2018;59:55–6.
53. Wittczak T, Dudek W, Walusiak-Skorupa J, Świerczyńska-Machura D, Pałczyński C. Chlorhexidine–still an underestimated allergic hazard for health care professionals. Occup Med (Lond). 2013;63:301–5.
54. Sato K, Kusaka Y, Suganuma N, Nagasawa S, Deguchi Y. Occupational allergy in medical doctors. J Occup Health. 2004;46:165–70.
55.• Nagendran V, Wicking J, Ekbote A, Onyekwe T, Garvey LH. IgE-mediated chlorhexidine allergy: a new occupational hazard? Occup Med (Lond). 2009;59:270–2 **Important study about the occupational risk of chlorhexidine allergy.**
56. Ibler KS, Jemec GBE, Garvey LH, Agner T. Prevalence of delayed-type and immediate-type hypersensitivity in healthcare workers with hand eczema. Contact Dermatitis. 2016;75:223–9.
57. Garvey LH, Roed-Petersen J, Husum B. Is there a risk of sensitization and allergy to chlorhexidine in health care workers? Acta Anaesthesiol Scand. 2003;47:720–4.
58. Garvey LH, Roed-Petersen J, Husum B. Anaphylactic reactions in anaesthetised patients—four cases of chlorhexidine allergy. Acta Anaesthesiol Scand. 2001;45:1290–4.
59.•• Garvey LH, Krøigaard M, Poulsen LK, Skov PS, Mosbech H, Venemalm L, et al. IgE-mediated allergy to chlorhexidine. J Allergy Clin Immunol. 2007;120:409–15 **A study where it was shown that chlorhexidine allergy is IgE mediated.**
60. Jee R, Nel L, Gnanakumaran G, Williams A, Eren E. Four cases of anaphylaxis to chlorhexidine impregnated central venous catheters: a case cluster or the tip of the iceberg. Br J Anaesth. 2009;103:614–5.
61. Dyer JE, Nafie S, Mellon JK, Khan MA. Anaphylactic reaction to intraurethral chlorhexidine: sensitisation following previous repeated uneventful administration. Ann R Coll Surg Engl. 2013;95:e105–6.
62. Kroigaard M, Garvey LH, Menne T, Husum B. Allergic reactions in anaesthesia: are suspected causes confirmed on subsequent testing? Br J Anaesth. 2005;95:468–71.
63. Christiansen IS, Krøigaard M, Mosbech H, Skov PS, Poulsen LK, Garvey LH. Clinical and diagnostic features of perioperative hypersensitivity to cefuroxime. Clin Exp Allergy. 2015;45:807–14.
64. Aschenbrenner DS. Rare allergic reaction to topical chlorhexidine gluconate. Am J Nurs. 2017;117:20.
65. Guleri A, Kumar A, Morgan RJ, Hartley M, Roberts DH. Anaphylaxis to chlorhexidine-coated central venous catheters: a case series and review of the literature. Surg Infect. 2012;13:171–4.
66. Loveday HP, Wilson JA, Pratt RJ, Golsorkhi M, Tingle A, Bak A, et al. Epic3: national evidence-based guidelines for preventing healthcare-associated infections in nhs hospitals in England. J Hosp Infect. 2014;86(S1):S1–70.
67. Geng V, Cobussen-Boekhorst H, Farrell J, Gea-Sánchez M, Pearce I, Schwennesen T, et al. (2012) Catheterisation. Indwelling catheters in adults, urethral and suprapubic. Eur Assoc Urol Nurses;112.

68. European Association of Urology. https://uroweb.org/guideline/urological-infections/.
69. Williams C. Making a choice of catheterisation gel and the role of chlorhexidine. Br J Community Nurs. 2017;22:346–51.
70. Stephens R, Mythen M, Kallis P, Davies DW, Egner W, Rickards A. Two episodes of life-threatening anaphylaxis in the same patient to a chlorhexidine-sulphadiazine-coated central venous catheter. Br J Anaesth. 2001;87:306–8.
71. Khoo A, Oziemski P. Chlorhexidine impregnated central venous catheter inducing an anaphylatic shock in the intensive care unit. Heart Lung Circ. 2011;20:669–70.
72. Chong HY, Lai NM, Apisarnthanarak A, Chaiyakunapruk N. Comparative efficacy of antimicrobial central venous catheters in reducing catheter-related bloodstream infections in adults: abridged cochrane systematic review and network meta-analysis. Clin Infect Dis. 2017;64(suppl_2):S131–40.
73. Centers for Disease Control and Prevention recommendation of chlorhexidine impregnated central venous catheters when it is expected to be there for more than five days. https://www.cdc.gov/infectioncontrol/guidelines/bsi/recommendations.html. Accessed 24 Feb 2019.
74. Guidelines on the Perioperative Management of Patients with Suspected or Proven Hypersensitivity to Chlorhexidine. Australian and New Zealand Anaesthetic Allergy Group (ANZAAG). http://www.anzca.edu.au/documents/ps60bp-2015-guidelines-on-the-perioperative-manage.pdf. Accessed 24 Feb 2019.
75. Chen P, Huda W, Levy N. Chlorhexidine anaphylaxis: implications for post-resuscitation management. Anaesthesia. 2016;71:242–3.
76. Brockow K, Garvey LH, Aberer W, Atanaskovic-Markovic M, Barbaud A, Bilo MB, et al. Skin test concentrations for systemically administered drugs—an ENDA/EAACI Drug Allergy Interest Group position paper. Allergy. 2013;68:702–12.
77. Mertes PM, Malinovsky JM, Jouffroy L, Aberer W, Terreehorst I, Brockow K, et al. Reducing the risk of anaphylaxis during anesthesia: 2011 updated guidelines for clinical practice. J Investig Allergol Clin Immunol. 2011;21:442–53.
78. Brockow K, Romano A, Blanca M, Ring J, Pichler W, Demoly P. General considerations for skin test procedures in the diagnosis of drug hypersensitivity. Allergy. 2002;57:45–51.
79. Fisher MM, Bowey CJ. Intradermal compared with prick testing in the diagnosis of anaesthetic allergy. Br J Anaesth. 1997;79:59–63.
80.• Anderson J, Rose M, Green S, Fernando SL. The utility of specific IgE testing to chlorhexidine in the investigation of perioperative adverse reactions. Ann Allergy Asthma Immunol. 2015;114:425–426.e1 **Study investigating the value of specific IgE to chlorhexidine.**
81. Leysen J, Bridts CH, De Clerck LS, Vercauteren M, Lambert J, Weyler JJ, et al. Allergy to rocuronium: from clinical suspicion to correct diagnosis. Allergy. 2011;66:1014–9.